IJPSR (2022), Volume 13, Issue 8 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 05 December 2021; received in revised form, 08 January 2022; accepted, 28 April 2022; published 01 August 2022

HYPERTROPHIC CARDIOMYOPATHY

P. Soni Dixitha *, M. Vijaya Bhargavi and M. Sumakanth

Department of Pharmaceutical Chemistry, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad - 500027, Telangana, India.

Keywords:

Cardiomyopathy, Hypertrophic, Death, Sudden, Cardiac heart failure, Human mutations, Myosin heavy chains

Correspondence to Author:
Ms. P. Soni Dixitha

Assistant professor,
Department of Pharmaceutical Chemistry, RBVRR Women's College of Pharmacy, Barkatpura, Hyderabad - 500027, Telangana, India.

E-mail: sonidixitha@gmail.com

ABSTRACT: Hypertrophic cardiomyopathy (HCM) is a genetic disorder that is characterized by left ventricular hypertrophy unexplained by secondary causes and a nondilated left ventricle with preserved or increased ejection fraction. It is commonly asymmetrical, with the most severe hypertrophy involving the basal interventricular septum. The histological features of HCM include myocyte hypertrophy and disarray, and interstitial fibrosis. Hypertrophy is also frequently associated with left ventricular diastolic dysfunction. It is also an important cause of sudden cardiac death, particularly in adolescents and young adults. Non-sustained ventricular tachycardia, syncope, a family history of sudden cardiac death, and severe cardiac hypertrophy are major risk factors for sudden cardiac death. Atrial fibrillation is also a common complication and is not well tolerated. Mutations in over a dozen genes encoding sarcomere-associated proteins cause HCM. MYH7 and MYBPC3, encoding β-myosin heavy chain and myosin-binding protein C, respectively, are the 2 most common genes involved.

INTRODUCTION: Hypertrophic cardiomyopathy (HCM) is a heterogeneous myocardial disease, most often caused by autosomal dominant sarcomeric gene mutations, representing the most common monogenic cardiomyopathy in humans. It is characterized by increased left ventricular wall thickness (hypertrophy), which causes left ventricular outflow obstruction, diastolic dysfunction, myocardial ischemia, mitral regurgitation, hyper myocardial contractility and reduced myofibrillar compliance disarray and fibrosis [2, 3]. These structural and functional abnormalities can produce fatigue, dyspnoea, chest pain, palpitations and syncope [4, 5, 6]. The ESC (European Society of Cardiology) defines HCM as "the presence of increased left ventricular (LV) wall thickness that is not solely explained by flow-limiting coronary artery disease (CAD) or abnormal loading conditions [7]. Other characteristic pathological features are myocardial fiber hypertrophy, disorganized myocardial cells, interstitial fibrosis and thickened intramyocardial coronary vessels.

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DOI: 10.13040/IJPSR.0975-8232.13(8).3043-55

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(8).3043-55

Types of HCM: The main classification of HCM is obstructive and non-obstructive HCM. Further, obstructive HCM can be described as sub-aortic and mid-ventricular based on the site of obstruction. On the other hand, non-obstructive HCM can be described as a normal systolic function or impaired systolic function. **Fig. 1** provides an illustration of the main and sub-classifications of HCM.

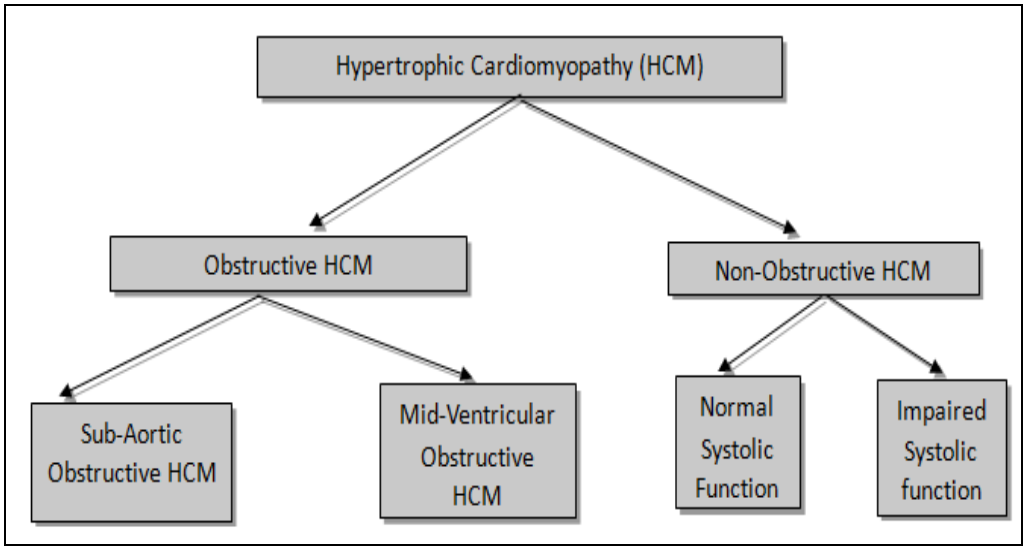


FIG. 1: FORMS OF HYPERTROPHIC CARDIOMYOPATHY

Systolic opposition of the mitral leaflet against the septum produces sub-aortic obstruction, while muscular opposition in mid-ventricular area produces midventricular obstruction.

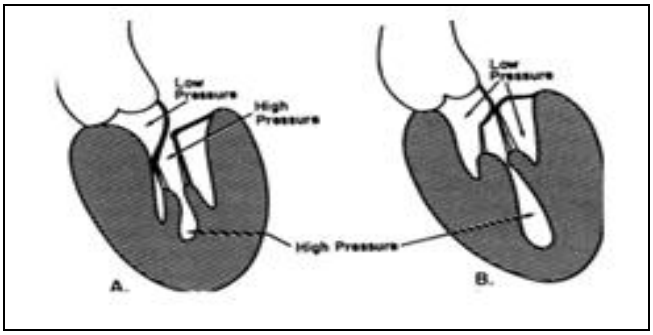


FIG. 2: (A) SUB-AORTIC AND MID-VENTRICULAR (B) OBSTRUCTIVE HCM

There are two possible sites of obstructive HCM. (A) Sub-aortic obstructive HCM is produced by apposition of the mitral leaflet against the septum. (B) Mid-ventricular obstructive HCM produced by muscular apposition in the mid-ventricular region.

Sub-aortic Obstructive HCM: Sub-aortic obstructive HCM results from a combination of basal septal thickening, anterior displacement of the mitral valve, and systolic anterior motion of the mitral valve contributing to LV outflow tract obstruction. The first is venturi forces, which result from the narrowing of LV outflow tract and subsequent increase in velocity and a decrease in pressure above the mitral valve causing the valve to displace towards the septum. The second is flow drag. Flow drag leads to the gradual development of systolic anterior motion of the mitral valve [8].

Mid-ventricular Obstructive HCM: Falicov and Resnekov were the first to describe mid-ventricular obstructive HCM in 1977. It is a rare form of HCM with an hourglass-shaped LV cavity and distinct apical chamber [8]. Echocardiographic systolic pressure at the apical chamber is elevated but normal above themid-ventricular obstruction compared to sub-aortic obstructive HCM, where the systolic pressure is elevated in the entire LV cavity. Mid-ventricular obstructive HCM also does not present with mitral insufficiency but has a greater symptom burden, an indicator of disease progression and end-stage HCM and is a predictor of HCM-related sudden death and lethal arrhythmias [9, 10].

Non-Obstructive HCM:

Normal / Impaired Systolic Function: Non-obstructive HCM is clinically defined as a variant of HCM characterized by the absence of LV outflow tract obstruction [8]. Its main classification are HCM with normal or impaired systolic function (end-stage phase). Depressed LV systolic function could result from myocardial ischemia and infarction due to many of non-obstructive HCM patients present with myocardial fibrosis.

Patients with non-obstructive HCM present with severe symptoms due to diastolic dysfunction and microvascular ischemia. These symptoms are difficult to treat and manage because of the lack of LV outflow tract obstruction. There are some factors which contribute LV outflow obstruction **Table 1.**

TABLE 1: FACTORS CONTRIBUTING TO LV OUTFLOW TRACT OBSTRUCTION

Causes	Main Characteristic
Anatomical Causes	Basal septal thickness
Mitral valve displaced anteriorly	muscles
Mitral valve systolic anterior motion	Elongated mitral valve
Abnormal insertion of the papillary	Abnormal cooptation of the mitral valve leaflets
Hemodynamic Causes	Rapid early LV ejection Venturi forces acting on anterior mitral valve leaflet Flow drag

Apical Hypertrophic Cardiomyopathy: Apical HCM is another relatively rare variant of non-obstructive HCM characterized by thickening of the myocardium in the left ventricular apex [11]. About 10% of the patients will present with apical infarction in the absence of coronary artery disease (CAD), which may result in the formation of an apical aneurysm. The formation of apical aneurysms is associated with sudden cardiac death, progressive heart failure, and thromboembolic events. At the same time, sudden cardiac death is less likely in isolated apical HCM [12].

Clinical Symptoms: The main clinical signs and symptoms of HCM are dependent upon the pathophysiologic processes leading to the development of HCM. **Fig. 3** illustrates the clinical symptoms and their association with pathophysiologic processes of HCM. Lethal arrhythmias, such as atrial fibrillation and sustained ventricular arrhythmias, contribute to stroke symptoms, syncope and sudden cardiac death [13].

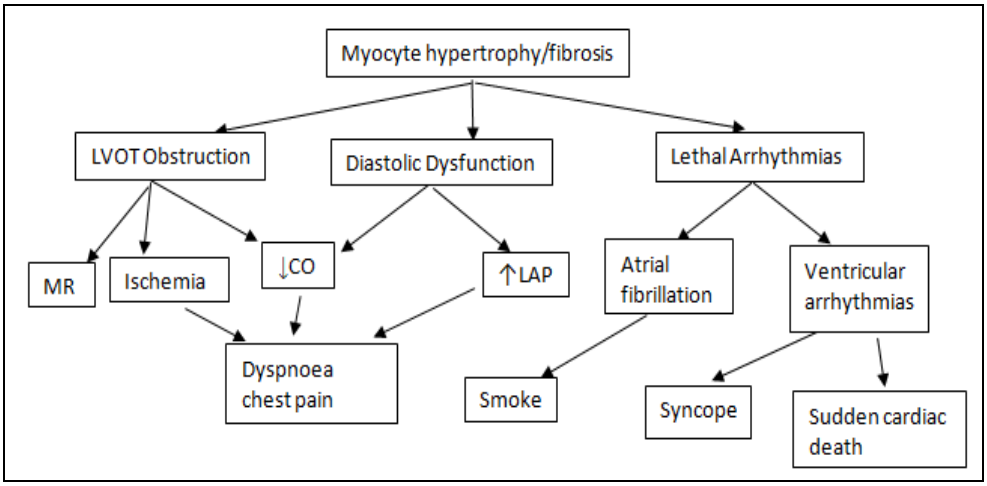


FIG. 3: CLINICAL SYMPTOMS AND ASSOCIATED PATHOPHYSIOLOGIC PROCESSES

The pathobiology mechanisms of HCM (LVOT obstruction, diastolic dysfunction and lethal arrhythmias in yellow) are associated with clinical symptoms of HCM: mitral regurgitation, ischemia, reduced cardiac output, increased left atrial pressure, atrial fibrillation, ventricular arrhythmias in green) and dyspnoea, stroke, syncope, and sudden cardiac death in blue). MR: Mitral regurgitation; CO: Cardiac Output; LAP: Left Atrial Pressure; LVOT: Left Ventricular Outflow Tract.

Sudden Cardiac Death: Sudden cardiac death is death from cardiac causes that occur within an hour of the onset of symptoms [14]. In the absence of other causative factors, sudden cardiac death is a significant clinical indicator for the clinical progression of HCM. Microvascular disorders may cause the development of myocardial fibrosis and ischemia and increase the predisposition of HCM patients to lethal arrhythmias, especially atrial fibrillation and ventricular arrhythmias. Sudden cardiac death indicates increasing frequency, prolongation, or sustenance of these lethal arrhythmias.

Atrial Fibrillation: Atrial fibrillation refers to supraventricular arrhythmia with characteristic chaotic atrium contraction [14]. In HCM patients, atrial fibrillation affects 20%, associated with an elevated risk of stroke, sudden cardiac death, and heart failure.

Diagnosis: The 2014 ECS guidelines on diagnosis and management of HCM developed a standardized diagnostic work-up, which involves laboratory testing, family screening, electrocardiography (ECG), echocardiography (echo) and cardiac

magnetic resonance imaging (MRI), and genetic testing [7]. The primary diagnostic criteria is the presence of LV hypertrophy defined by LV wall thickness ≥ 15 mm measured by any imaging modality: echo, cardiac MRI, or cardiac CT in the absence of any abnormal loading condition. Diagnostic procedures should include other tests such as family history, ECG abnormalities, non-cardiac symptoms and multimodal cardiac MRI [7]. Clinical diagnosis of HCM is established most easily and reliably with 2-dimensional echocardiography by imaging the hypertrophied but non-dilated LV chamber, in the absence of another cardiac or systemic disease (ex: hypertension or aortic stenosis) capable of producing the magnitude of hypertrophy evident **Fig. 4** (occasionally during participation sports examinations), new symptoms or abnormal ECG pattern.

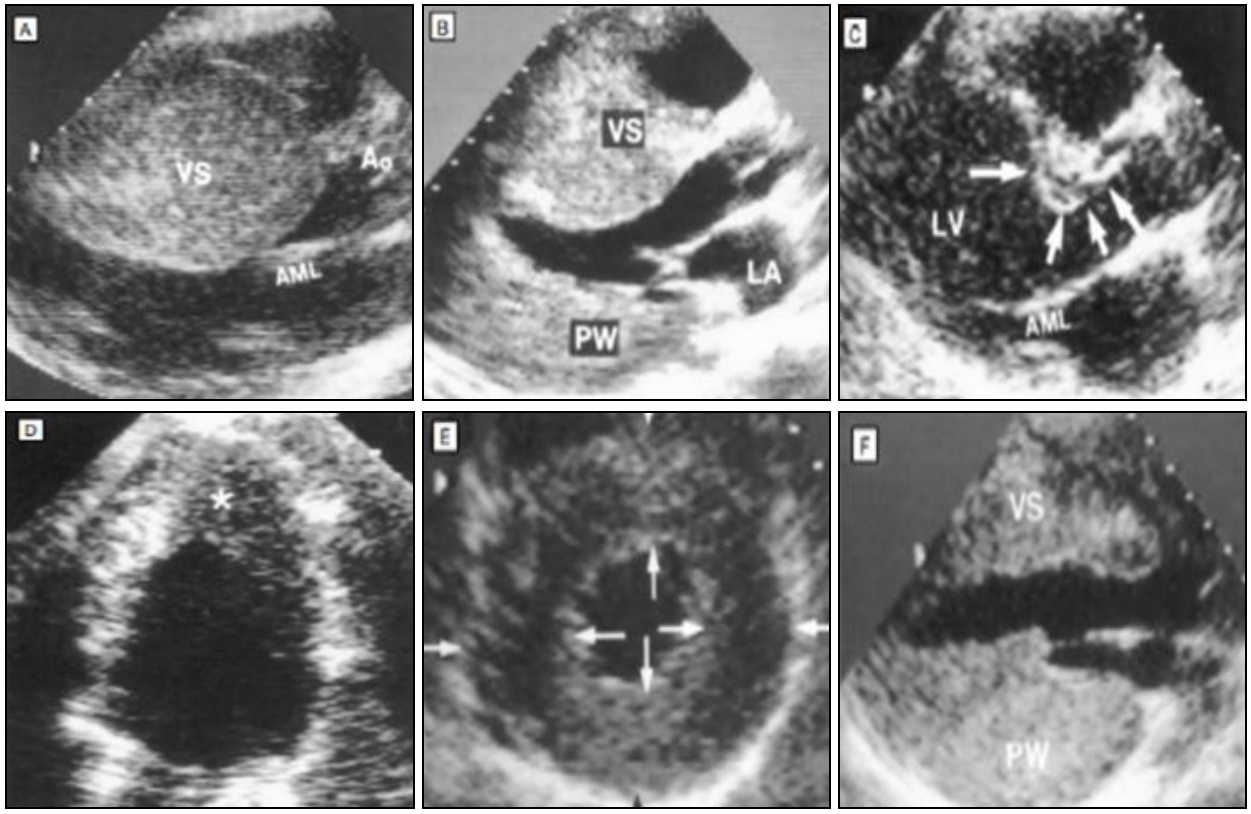


FIG. 4: HETEROGENEITY IN THE PATTERN AND EXTENT OF LEFT VENTRICULAR (LV) WALL THICKENING IN HCM

Echocardiographic parasternal long-axis stop-frame images obtained in diastole showing A, massive asymmetric hypertrophy of ventricular system (VS) with wall thickness >50mm; B, pattern of septal hypertrophy in which the distal portion is considerably thicker than the proximal region at mitral(arrows); D, hypertrophy confined to LV apex, consistent with the designation of apical hypertrophic cardiomyopathy (HCM); E, relatively mild hypertrophy in a concentric (symmetric) pattern with each segment of ventricular septum and LV free wall showing similar or identical thickness; F, inverted pattern of hypertrophy in which anterior VS is less subsequently thickened than the posterior free wall (PW), which is markedly hypertrophied (*i.e.,* 40mm). Ao indicates Aorta; AML, anterior mitral leaflet and LA, left atrium.

Family History: Family history provides important information for patients with a diagnostic possibility of HCM, particularly in a family with a history of heart disease at young age [16]. Analysis of family history involves constructing 3-4 generations of family pedigree. Pedigree analysis should focus on incidents and age of presentation of sudden cardiac deaths, heart failure, heart transplantation and stroke [7]. Pedigree analysis provides valuable information on the pattern of inheritance.

Physical Examination: The physical examination may not be a reliable method for clinical identification, and most patients do not have LV outflow tract obstruction. HCM patients are asymptomatic and diagnosis is incidental during screening. Some HCM patients present with symptoms such as exertional angina, dyspnoea, syncope, and palpitations. In addition to these symptoms, general physical extermination provides information about non-cardiac symptoms useful for specific diagnosis such as syndromic or metabolic etiologies. Physical examination is usually normal in asymptomatic patients without LVOT obstruction. **Table 2** explains a summary of signs and symptoms suggesting the specific diagnosis. Some maneuvers modify the intensity of the murmur and assist in the clinical diagnosis of the disease **Table 3.**

TABLE 2: SIGNS AND SYMPTOMS SUGGESTING SPECIFIC DIAGNOSTIC CLUES

Signs and Symptoms	Specific Diagnostic Clues
Learning difficulties/mental retardation	Mitochondrial disease, Danon disease, syndromic disease (Noonan/LEOPARD)
Sensor neural deafness	Mitochondrial disease with diabetes, Anderson-Fabry disease, LEOPARD Syndrome.
Visual impairment	Mitochondrial disease, Amyloidosis, Danon disease and Anderson-Fabry disease
Gait disturbance	Friedreich's ataxia
Sensory abnormalities	Amyloidosis, Anderson-Fabry disease
Muscle weakness	Mitochondrial disease, Friedreich's ataxia, glycogen storage disorders
Palpebral ptosis	Mitochondrial disease, Noonan/ LEOPARD syndrome
Angiokeratomata, hypohidrosis	Anderson-Fabry disease

TABLE 3: EFFECTS OF INTERVENTIONS ON THE LVOT GRADIENT AND MURMUR IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Intervention murmur	Gradient and cardiac
Valsalva manoeuvre	Increase
Orthostatic position	Increase
Post extrasystole	Increase
Squatting Position	Decrease
Handgrip manoeuvre	Decrease

Electrocardiography: Electrocardiography (ECG) is the recommended initial test for known or suspected HCM at rest and during exercise. Various combinations of ECG abnormalities such as Q-waves, LVH, ST- and T- waves could suggest important diagnostic clues of HCM.

Electrocardiographic abnormalities **Fig. 5** are nearly ubiquitous in HCM patients. While its high sensitivity makes the ECG an optimal screening test, the abnormalities are varied and non-specific. Typically, the ECG reveals prominent voltages with localized or widespread repolarization abnormalities. Other abnormalities include prominent inferior or lateral Q-waves, left axis deviation, and p-wave abnormalities, including left or right atrial abnormalities. Pseudo-delta waves may also be seen, mimicking the pre-excitation syndromes (*e.g.,* Wolff Parkinson White syndrome). **Table 4** explains a summary of ECG findings suggesting a specific diagnosis of HCM.

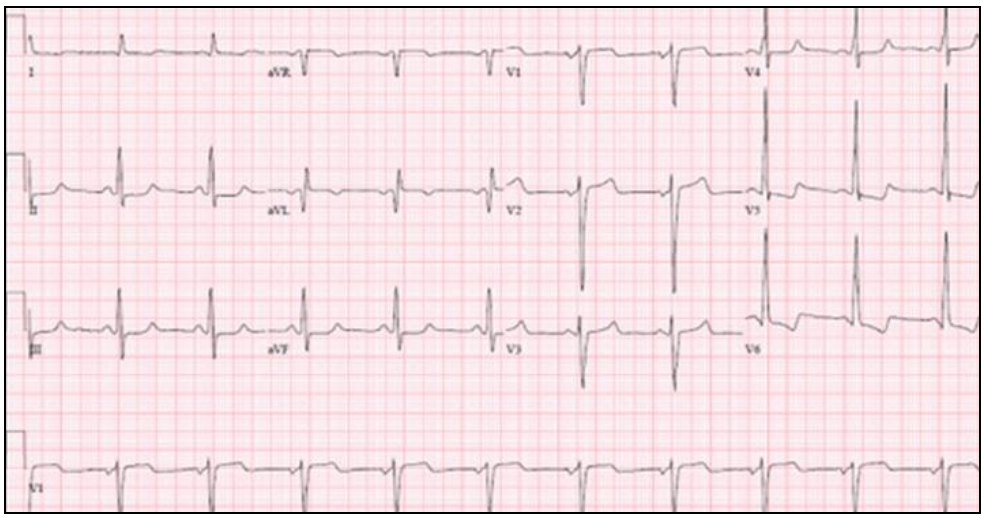


FIG. 5: ECG OF A 51-YEAR-OLD PATIENT WITH HCM. NOTE THE PROMINENT PRECORDIAL VOLTAGE, WIDESPREAD REPOLARIZATION ABNORMALITIES, Q-WAVE IN THE LATERAL LEAD (AVL), AND P-WAVE ABNORMALITY, SUGGESTING LEFT ATRIAL ENLARGEMENT

TABLE 4: ECG FINDINGS SUGGESTING SPECIFIC DIAGNOSIS

Signs and Symptoms Specific Diagnostic Clues [33]
Pre-excitation Storage disease and mitochondrial disorders
Short PR without preexcitation Storage diseases (Anderson-Fabry disease)
AV block Mitochondrial disorders, some storage disease (Anderson-Fabry disease), amyloidosis and desminopathies
Severe LV hypertrophy (Sokolow score ≥ 50)Storage disease (Pompe and Danon)
Low QRS voltage AL/TR amyloidosis
Extreme QRS axis deviation Syndromic disease (Noonan syndrome) with severe basal hypertrophy
Giant negative T-wave >10 mm Involvement of LC apex
Abnormal Q-wave Asymmetric LV distribution
ST-segment elevation Apical or distal hypertrophy

The most common abnormalities are ST-segment and T-wave changes. Other electrocardiographic alterations may be present in HCM as shown in **Table 5.**

TABLE 5: ECG FEATURES OF HCM

ECG abnormalities of HCM
Presence of deep S waves in V1 and V2 and large R waves in V5 and V6 strain repolarisation changes.
Pathological Q waves in the inferior and lateral leads with ≥ 40ms durations and ≥ 3mm in depth suggest LV asymmetric septal hypertrophy. Lateral Q waves are more common than inferior Q waves in HCM. Occur in 20 to 50% of patients and are attributed to septal hypertrophy
P-Wave abnormalities related to left atrial overload (duration > 120 ms, notch P-wave mitrale, Morris index) can be observed
pre-excitation syndrome is observed in a glycogen-storage disease produced by LAMP2 or PRKAG2 mutations or Anderson-Fabry disease
Atrial fibrillation supraventricular tachycardias are common ventricular dysrhythmias (e.g. VT) also occur and may be a cause of sudden death
Apical HCM
Giant negative T waves in precordial leads suggest HCM of the LV apex, initially described in Japan and called yamagushi

Imaging: Echocardiography: Imaging takes a central role in establishing both diagnosis and prognosis in HCM. The diagnosis of HCM rests on the detection of increased LV wall thickness by any imaging modality in the absence of another cardiac or systemic disease that itself would be capable of producing the magnitude of hypertrophy [17, 18].

Echo is used to measure LV outflow tract obstruction defined by LV outflow tract pressure gradient ≥ 50 mm Hg. 2-D and Doppler echo are used to determine the severity and mechanism of LV outflow tract obstruction. When non-invasive images lack clarity, transoesophageal echo (TEE) or transthoracic echo (TTE) may be considered in selected patients [19]. **Table 6** explains a summary of echo findings alongside their diagnostic clues. Transthoracic echocardiography has been the mainstay for imaging the HCM phenotype, and it remains the initial test for patients due to its portability, widespread access, and reliability in quantifying dynamic outflow tract gradients **Fig. 6** [23].

It can also determine changes in the mitral valve and the follow-up of the disease. The presence of LVH (>15 mm LV wall thickness in diastole) in the absence of another cause confirms the diagnosis [20-22]. Echocardiography findings can differentiate different patterns of LV hypertrophy and LVOT gradient and velocity.

TABLE 6: ECHO FINDINGS SUGGESTING SPECIFIC DIAGNOSIS

Signs and Symptoms Specific Diagnostic Clues
Increased inter-atrial septum thickness Amyloidosis
Increased AV valve thickness Amyloidosis, Anderson-Fabry disease
Increased RV wall thickness Amyloidosis, Anderson-Fabry disease, myocarditis, Noonan syndrome
Mild-moderate pericardial effusion Amyloidosis, myocarditis
Concentric LVHGlycogen storage disease, Anderson-Fabry disease
Severe Concentric LVH (≥ 30 mm)Danon disease, Pompe disease
Global LV hypokinesia Mitochondrial disease, Amyloidosis, Danon disease, myocarditis, Anderson-Fabry disease
RV ObstructionNoonan syndrome and associated abnormalities

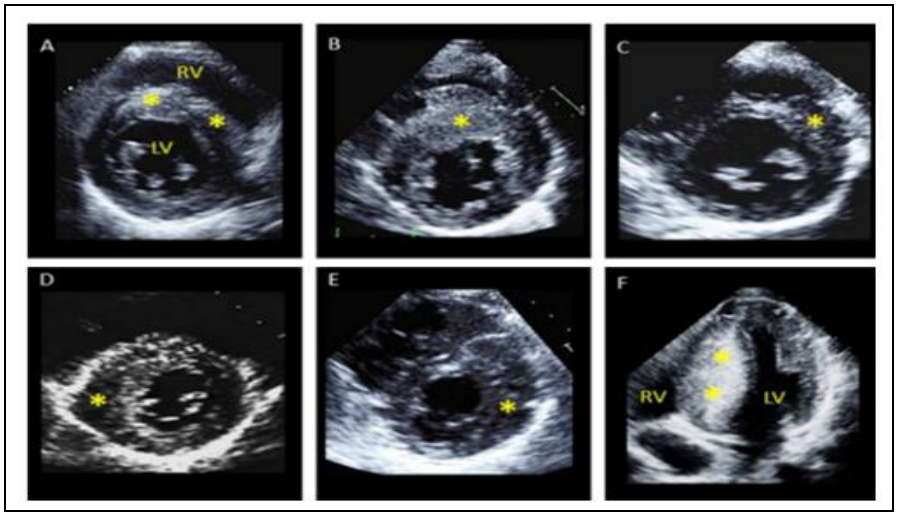


FIG. 6: ECHOCARDIOGRAPHIC IMAGES SHOWING PATTERNS OF LV HYPERTROPHY

Patterns of LV hypertrophy. (A) LV hypertrophy involves the entire basal septum. (B) Marked LV hypertrophy of the anterior septum. (C) LV hypertrophy of the septum-anterior wall junction. (D)LV hypertrophy limited to the sepal-posterior wall. (E) Anterior LV free wall thickening. (F) Massive LV hypertrophy of the entire septum from basal to apical regions.

One advantage of 2D echocardiography is the ability to evaluate the ventricular, valvular, and outflow states under various provocative maneuvers, most commonly exercise. Echocardiography uses continuous wave, pulse wave, and color Doppler techniques to estimate outflow tract gradients and valvular regurgitation. Other abnormalities include prominent inferior or lateral Q-waves, left axis deviation, and p-wave abnormalities, including left or right atrial abnormalities. Pseudo-delta waves may also be seen mimics the preexcitation syndrome.

Cardiac Magnetic Resonance: Several imaging modalities of cardiac magnetic resonance imaging (MRI) provides detailed diagnostic information about cardiac morphology and ventricular function as well as characterize myocardial tissue in HCM patients. It can also be performed for the differential diagnosis of myocardial hypertrophies found in other situations, such as athlete's heart, hypertensive heart disease, and deposition diseases (Fabry's disease and amyloidosis). Cardiac MRI also provides additional information to define apical or aneurysm and suggests the need for alternative diagnoses for underlying disorders such as Anderson-Fabry disease and genetic phenocopies. Cardiac MRI is indicated for diagnosis and assessment of concurrent cardiac disorders. Late gadolinium enhancement (LGE) MRI has been shown to correlate with cardiac death and heart failure, but evidence is inconclusive of its value in predicting sudden cardiac death in HCM patients [24]. CMR identifies myocardial fibrosis, found in up to 65% of HCM patients, with often multifocal, irregular distribution and not respecting coronary anatomy [25-27]. Cardiac MRI is useful in the differential diagnosis of HCM to suggest specific diagnoses based on magnetic properties, distribution and degree of interstitial expansion. Cardiac MRI images improve the assessment of LV hypertrophy, especially in the anterolateral LV free wall. **Fig. 7** illustrates cardiac MRI images of different severity of LV hypertrophy in HCM patients.

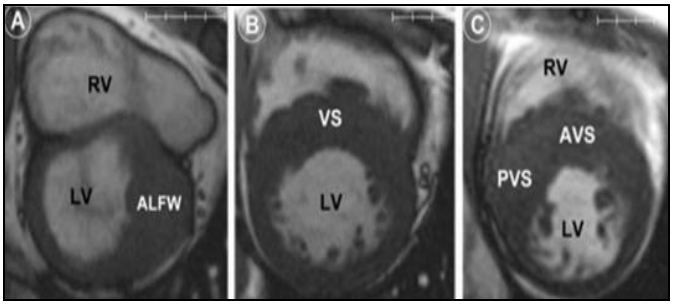


FIG. 7: CARDIAC MRI IMAGES SHOWING PATTERNS OF LV HYPERTROPHY

HCM has diverse patterns of LV hypertrophy as indicated by cardiac MRI short axis at the end of diastole. (A) shows LV hypertrophy at the anterolateral free wall (ALFW) transitioning sharply to the normal wall thickness at the anterior septum and posterior free wall. (B) Moderate LV

hypertrophy at anterior and posterior portions of the ventricular septum (VS). (C) Predominant posterior ventricular septal hypertrophy (PVS) that extends to anterior ventricular septum (AVS).

Nuclear Imaging: Nuclear imaging can provide measurements of LV volumes and ejection function, RV volumes and ejection function, and identify thickened myocardium without a definable cause and myocardial ischemia **Table 7.**

TABLE 7: NUCLEAR IMAGING EVALUATION OF PATIENTS WITH HCM

1	Myocardial Perfusion
2	LV volumes and ejection function by radionuclide and gated SPECT
3	Coronary flow reserve by PET
4	Cardiac metabolism by PET (research application)

The use of nuclear imaging is not very common, but it has been used to assess myocardial blood flow and defects in myocardial perfusion in HCM patients [28]. The major contribution of nuclear imaging to the diagnosis of HCM is the detection of TTR-induced cardiac amyloidosis. TTR is a plasma transport protein produced in the liver and a precursor in the development of systemic and TTR-related amyloidosis [29, 30]. In addition, the degree of microvascular dysfunction in patients with HCM was assessed by Positron Emission Tomography (PET).

Genetic Testing: HCM has been associated with eleven or more genes having more than 1000 mutations [31]. Of these, mutations in genes encoding β-myosin heavy chain and cardiac myosin binding protein C account for ≥ 50% of mutations in HCM. Genetic testing has proved during family screening.

HCM is usually diagnosed using non-invasive methods, without the need for endomyocardial biopsy (EMB) [32]. **Table 8** summarizes the recommendations of the main imaging techniques in patients with suspected HCM.

TABLE 8: IMAGING TECHNIQUES IN PATIENTS WITH SUSPECTED HCM

Imaging techniques Recommendations
Genetic testing and counselling should be performed on all HCM patients. Genetic screening should be performed in all first-degree relatives of patients with a specific mutation
Electrocardiogram (ECG) Initial evaluation and with worsening symptoms. It can also perform as a screening of family members, every12-18 month when it does not identify the presence of ventricular hypertrophy on the initial cardiogram
Exercise testing Assessment of functional capacity and therapeutic respon. Risk stratification of SCD Assessment of the systolic blood pressure Assessment of latent obstructive forms when associated with echocardiogram
Ambulatory ECG monitoring Recommended for risk stratification of SCD (e.g.,Ventricular tachycardia) and stroke (e.g., Atrial fibrillation)
Transthoracic echocardiography Diagnosis and monitoring of HCM patients Screening of family members in the absence of genetic mutation in the index case from 12-years old and repeated every 12-18 months. Detection of systolic anterior motion of the mitral valve (SAM) with 2-D and M-echocardiography
Cardiac Magnetic resonance Inadequate echocardiography window and poor myocardial segment visualisation. Additional assessment of hypertrophy (distribution and location) and anatomy of the mitral valve and detection of papillary muscle abnormalities. Differential diagnosis of other heart diseases such as amyloidosis, Fabry disease and LAMP2. Detection of the presence of apical aneurysm. Assessment of myocardial fibrosis for risk stratification for SCD

Molecular Pathogenesis of HCM: The pathogenic mechanisms by which HCM-associated mutations cause the disease remain unclear and controversial. Impaired myofibrillar contractile function was initially suggested to be the most important mechanism, accounting for 'compensatory' hypertrophy and diastolic dysfunction two hallmarks of the clinical phenotype. Clinical and pathological manifestations of HCM, including perturbations in calcium cycling and sensitivity, increased myocardial fibrosis, altered sensing of biomechanical stress, impaired energy homeostasis, and microvascular dysfunction **Fig. 8.**

A. Disturbed biomechanical stress sensing. B. Impaired calcium cycling and sensitivity. C. Altered energy homeostasis. D. Increased fibrosis. These pathways should not be considered in isolation because they can act in concert (for example, metabolic deficits and impaired calcium cycling). Abbreviations: LTCC, voltage-dependent L-type calcium channel; PLB, cardiac phospholamban; RyR2, ryanodine receptor 2; SERCA2, sarcoplasmic/endoplasmic reticulum calcium ATPase 2; SR, sarcoplasmic reticulum; TGF-β, transforming growth factor β; T-tubule, transverse tubule.

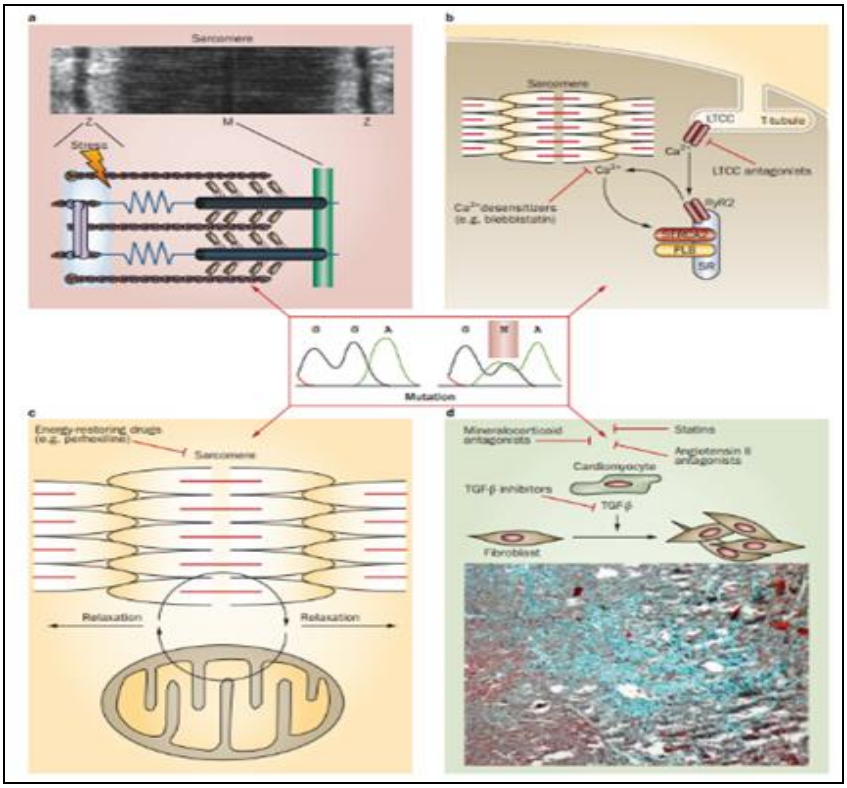


FIG. 8: DISEASE PATHWAYS OF HYPERTROPHIC CARDIOMYOPATHY AND POTENTIAL THERAPEUTIC INTERVENTIONS. VARIOUS SIGNALLING PATHWAYS AND DISEASE MECHANISMS CAN BE ACTIVATED AS THE RESULT OF A SPECIFIC GENE MUTATION

Impaired Calcium Cycling and Sensitivity: Impaired cardiomyocyte calcium cycling, for example, because of altered expression, phosphorylation, or both, of key proteins such as the sarcoplasmic/endoplasmic reticulum calcium ATPase 2 and the ryanodine receptor 2, is central to the pathogenesis of systolic and diastolic heart failure. Human cardiac muscle troponin T suggests that calcium cycling and homeostasis alterations might also contribute to ventricular arrhythmias in patients with HCM. Ventricular tachycardia could be reproduced by calcium-sensitizing agents, suggesting that myofibrillar calcium sensitization was likely to be the underlying molecular mechanism of the arrhythmias in this model of HCM. Blebbistatin, which decreases calcium sensitivity.

Increased Myocardial Fibrosis: Arrhythmias in patients with HCM are commonly attributed to an increase in left ventricular muscle mass, 54 myocyte disarray, or fibrosis. Fibrosis has been attributed to premature (apoptotic) death of myocytes and subsequent replacement by an expansion of the interstitial matrix resulting from microvascular ischemia, cardiomyocyte hypertrophy, or both. A role for nonmyocytes (most likely fibroblasts) in HCM-associated fibrosis has been suggested. The angiotensin-II receptor antagonist losartan diminished the development of fibrosis, consistent with the known role of angiotensin in promoting TGF-β expression. The progressive accumulation of collagen during replacement or scarring results in fibrosis that typically appears in a focal or patchy pattern. With gadolinium-based contrast agents, cardiovascular MRI detects these fibrotic areas with high spatial resolution. These areas are often detectable in segments of increased wall thickness. The synthesis of collagen is a complex process.

Procollagen molecules are produced within the endoplasmic reticulum of fibroblasts and secreted into the interstitial space, and they undergo cleavage of their end-terminal pro-peptide sequences by procollagen N-proteinase and C-proteinase to allow the formation of mature collagen fibers [33]. The activity of the fibrotic process can be quantified because the amount of cleaved C-terminal pro-peptide from type I procollagen (PICP) correlates with the amount of collagen deposited.

Microvascular Dysfunction: Microvascular dysfunction of the intramyocardial coronary arterioles can be observed in many patients with HCM and is characterized by intimal hyperplasia and medial hypertrophy that leads to thickening of the vessel wall and, ultimately, reduction of the intraluminal area [34]. Microvascular ischemia is regarded as a predictor of an unfavourable outcome in patients with HCM because it impairs systolic and diastolic function, which promotes the occurrence of arrhythmias.

Therapy: Profound advances have been achieved in the clinical therapy of HCM in both the management of symptoms and the prevention of life-threatening complications such as end-stage heart failure and sudden cardiac death.

Lifestyle Changes: In patients with HCM, attention to specific lifestyle changes can help mitigate symptoms and may reduce the risk of SCD (Sudden Cardiac Death). During exercise, not only is cardiac inotropy and chronotropy augmented, but systemic vascular resistance (SVR) decreases without the ability to augment cardiac output because of outflow obstruction resulting in systemic hypoperfusion [20].

Pharmacologic Therapy: Pharmacotherapy is the most frequently used therapy for HCM, mostly obstructive HCM. The mainstay of the therapy is a combination of three types of drugs: β-adrenergic antagonist, calcium channel blockers and antiarrhythmic drugs. These drugs act by slowing the heart rate to improve LV outflow tract obstruction and symptoms. A slow heart rate improves LV filling and decreases myocardial oxygen demand [13]. The current treatment regimen for HCM, both types, has a primary goal of improving symptoms and cardiac function using beta-blockers and other cardiovascular drugs such as verapamil, an anti-hypertensive and disopyramide an anti-arrhythmic.

β-Adrenergic antagonist: β-adrenergic antagonist was discovered in the 1960s as an effective sand drug in treating and managing obstructive HCM. Pharmacologic therapies for HCM have been shown to reduce physiologic outflow obstruction, angina, dyspnoea on exertion and the risk of ventricular arrhythmias. These effects are mediated by the reduction in heart rate leading to increased diastolic filling time, decreased inotropy and possibly a reduction in ventricular stiffness induced by the sympatholytic effects of beta-blockade [35].

Propranolol was first studied in four early trials. One trial compared nadolol (beta-blocker) to verapamil (non-dihydropyridine calcium channel blocker) and found nadolol superior in terms of symptomatic relief. For patients with inducible outflow obstruction, bisoprolol effectively reduces or abolishes any gradient on provocation.

Calcium Channel Blockers: The non-dihydropyridine calcium channel blockers (verapamil and diltiazem) are used similar to beta-blockers to reduce cardiac chronotropic and inotropy, leading to improved diastolic filling, reduced outflow gradient and improved perfusion of the subendocardium. Verapamil is a frequently prescribed calcium channel blocker, which improves LVOT gradient and diastolic function. Verapamil vasodilatory properties are associated with negative side effects such as hypotension, increased outflow gradient and pulmonary edema, limiting its prescription and actual use [13]. Using the non-dihydropyridine calcium channel blockers in patients with either severe outflow obstruction (because of their vasodilatory effect in the peripheral vasculature) or severe heart failure in non-obstructive disease (because of negative inotropy).

Antiarrhythmic Drugs: Antiarrhythmic drugs are a third class of drugs used to alleviate HCM-related symptoms. A frequently prescribed antiarrhythmic drug is disopyramide, which acts by producing a negative inotropic effect causing an improvement in resting LVOT gradient and alleviating heart failure symptoms even more than the β-adrenergic antagonist. In most cases, it is prescribed with β-adrenergic antagonist or calcium channel blockers to improve treatment and prognostic value.

Marketed Drugs:

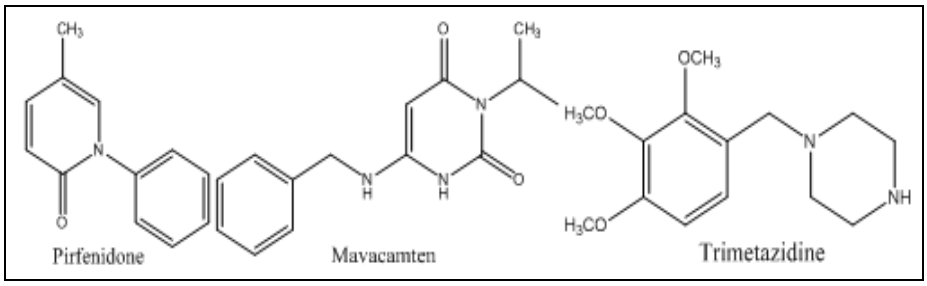
Pirfenidone: The effectiveness of the drug pirfenidone (Deskar) in improving heart function in patients with hypertrophic cardiomyopathy (HCM). Stiffening of the heart muscle in patients with HCM impairs the heart's ability to relax and thus fill and empty properly.

This can lead to heart failure, breathlessness and excessive fatigue. This study will test whether pirfenidone can reduce fibrosis, improve heart relaxation and reduce abnormal heart rhythms.

Mavacamten: Mavacamten will likely dominate the OHCM market as the first-in-class cardiac myosin inhibitor. Mavacamten has a significant advantage in entering the OHCM portion of the cardiovascular disease market as it is a first-in-class cardiac myosin inhibitor.

Trimetazidine: Trimetazidine is a reversible competitive inhibitor of 3-ketoacyl-coenzyme. Thiolase has a good safety and tolerability profile and improves exercise performance in patients with stable angina and ischemic cardiomyopathy.

Trimetazidine appears to reduce free radical production and prevents the accumulation of protons, sodium and calcium in the myocyte.



Different Treatments for Hypertrophic Cardio-myopathy:

Ayurvedic Treatment: The treatment of Hypertrophic cardiomyopathy (HCM) is mostly focused on slowing or regulating the heart rate. The common treatments of the disease include medications (diuretics, disopyramide, or beta-blockers), implantable cardiac defibrillator (for patients with certain kinds of heartbeat irregularities), and surgery (septal myectomy or heart transplant).HCM can also be managed effectively with the help of herbal products. Planet Ayurveda's herbal manufacturing company offers some beneficial herbal products for the natural management of heart disease. The products prepared under the guidance of professional Ayurveda practitioners.

1. Total Heart Support Capsules: The preparation of these capsules involves the use of standardized extracts of several potent herbs which are known for their medicinal significance. These herbs include Ashwagandha (*Withania somniferum*), Brahmi (*Bacopa monieri*), Arjuna (*Terminalia arjuna*), and Shankhapushpi (*Convolvulus pluricaulis)*. The use of the capsules is beneficial for patients suffering from HCM because of the ability of the capsules to manage heart disorders, support nervous control, keep the heart muscles healthy, detoxify the arteries of blockages, relieve stress and anxiety, support healthy blood pressure levels and balance *Vata* and *Pitta doshas* in the body.

Dosage: 2 capsules, two times a day.

2. Arjuna Capsules: These capsules are prepared from the bark extract of the 'Arjuna' tree (*Terminalia arjuna*). Arjuna is used widely for preparing several Ayurvedic formulations, especially those aimed at managing heart problems, high cholesterol and blood pressure. The use of these capsules can benefit HCM patients because of the ability of the Arjuna herb to maintain blood pressure and cholesterol levels, support heart muscles, improve blood circulation in the body, clear blocked arteries and manage venous thrombosis.

Dosage: 2 capsules, two times a day.

3. Curcumin Capsules: The preparation of these capsules involves the use of the 'Curcumin' compound of the rhizomatous herb of Turmeric (*Curcuma longa*). Therefore, each Curcumin capsule contains a standardized extract of Turmeric which has amazing medicinal properties. Turmeric is a common household spice that is widely known for its antioxidant and anti-inflammatory actions. Curcumin capsules are beneficial for people affected by HCM because the capsules can reduce inflammation, manage nerve pain, treat muscle aches, manage stiff and swollen joints, relieve

muscular disorders, and treat musculos-keletal diseases.

Dosage: 2 capsules, two times a day.

CONCLUSION: HCM is a sudden death-causing disease so there is the involvement of genetic mutations. This article provides the diagnosis, drugs used in the treatment, and various ayurvedic treatments available. So, there is a lot of scope for the research in this area.

ACKNOWLEDGEMENT: The authors would like to thank the principal and management of RBVRR Women's College of Pharmacy.

CONFLICTS OF INTEREST: The authors report no financial interest.

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How to cite this article:
Dixitha PS, Bhargavi MV and Sumakanth M: Hypertrophic cardiomyopathy. Int J Pharm Sci & Res 2022; 13(8): 3043-55. doi: 10.13040/IJPSR.0975-8232.13(8). 3043-55.